PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference E30095PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/10881	International filing date *(day/month/year)* 01.10.2003	Priority date *(day/month/year)* 01.10.2002
International Patent Classification (IPC) or both national classification and IPC C12Q1		
Applicant EPIGENOMICS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 13 sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.05.2004	17.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Pinta, V Telephone No. +31 70 340-4049

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/10881

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-67 as originally filed

Claims, Numbers

1-80 as amended (together with any statement) under Art. 19 PCT

Drawings, Sheets

1/23-23/23 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 2, 5-9, 11, 14, 16, 19, 26, 29, 31, 34, 63 and 66 (completely), 1, 3, 4, 10, 12, 13, 15, 17, 18, 20-25, 27, 28, 30, 32, 33, 35-62, 64, 65 and 67-80 (partially)

   because:

   ☒ the said international application, or the said claims Nos. 80 (partially) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 2, 5-9, 11, 14, 16, 19, 26, 29, 31, 34, 63 and 66 (completely), 1, 3, 4, 10, 12, 13, 15, 17, 18, 20-25, 27, 28, 30, 32, 33, 35-62, 64, 65 and 67-80 (partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1, 3, 4, 10, 12, 13, 15, 17, 18, 20-25, 27, 28, 30, 32, 33, 35-62, 64, 65 and 67-80 (all partially: invention 1) .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 3, 4, 10, 12, 13, 15, 17, 18, 20-24, 45-62, 64, 65, 67-77, 79, 80
	No:	Claims	25, 27, 28, 30, 32, 33, 35-44, 78
Inventive step (IS)	Yes:	Claims	1, 3, 4, 10, 12, 13, 15, 17, 18, 20-24, 45-62, 64, 65, 67-77
	No:	Claims	25, 27, 28, 30, 32, 33, 35-44, 78, 79, 80
Industrial applicability (IA)	Yes:	Claims	1, 3, 4, 10, 12, 13, 15, 17, 18, 20-25, 27, 28, 30, 32, 33, 35-62, 64, 65, 67-79
	No:	Claims	80

2. Citations and explanations

   see separate sheet

1 Reference is made to the following documents:

D1: LAPIDUS R G ET AL: "Methylation of estrogen and progesterone receptor gene 5' CpG islands correlates with lack of estrogen and progesterone receptor gene expression in breast tumors." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. MAY 1996, vol. 2, no. 5, May 1996 (1996-05), pages 805-810.

D2: OTTAVIANO Y L ET AL: "Methylation of the estrogen receptor gene CpG island marks loss of estrogen receptor expression in human breast cancer cells" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 54, no. 10, 15 May 1994 (1994-05-15), pages 2552-2555.

D3: WO 01/68912 A (PIEPENBROCK CHRISTIAN ; BERLIN KURT (DE); EPIGENOMICS AG (DE); OLEK AL) 20 September 2001 (2001-09-20).

D4: EP-A-1 167 975 (UNIV PARIS DESCARTES) 2 January 2002 (2002-01-02).

D5: CURMI P A ET AL: "Overexpression of stathmin in breast carcinomas points out to highly proliferative tumours" BRITISH JOURNAL OF CANCER, LONDON, GB, vol. 82, no. 1, 2000, pages 142-150.

D6: BRATTSAND G: "Correlation of oncoprotein 18/stathmin expression in human breast cancer with established prognostic factors." BRITISH JOURNAL OF CANCER. AUG 2000, vol. 83, no. 3, August 2000 (2000-08), pages 311-318.

D7: YAN P S ET AL: "Dissecting complex epigenetic alterations in breast cancer using CpG Island microarrays" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 61, no. 23, 1 December 2001 (2001-12-01), pages 8375-8380.

Re Item III

1 The subject-matter of claim 80 relates to the use of any of the methods or products claimed for the **treatment**, characterisation, classification and/or differentiation of **breast cell proliferative disorders**. Said claim covers therefore *inter alia* methods for treatment of the human body by therapy, which constitute subject-matter on which the IPEA is not required to carry out preliminary examination (Art. 34(4)(a)(I) PCT, Rule 67.1 (iii) PCT, PCT/GL/ISPE/1, 9.08-9.10).

Re Item IV

Lack of unity of invention

1 This IPEA agrees with the objection of lack of unity raised by the ISA. The reasons for this finding of non-unity, based on the concept linking the markers provided rather than on claim 1 alone, are as follows.

1.1 The single general concept underlying the present application has been defined as the provision of markers whose methylation status is useful for predicting the responsiveness of a subject with a cell proliferative disorder of the breast tissues to a therapy comprising one or more drugs that target the estrogen receptor pathway or are involved in estrogen metabolism, production or secretion.

1.2 D1 (Lapidus et al. (Clinical Cancer Research (1996) 2 (5): 805-810)) and D2 (Ottaviano et al. (Cancer Research (1994) 54: 2552-2555)) disclose such a marker: the estrogen receptor (ER) gene. Both documents indicate that the absence of ER expression is associated with extensive methylation of the ER gene 5' CpG island, and that said absence is also correlated with resistance to treatments targeting the estrogen pathway (see abstracts).

1.3 In view of said prior art documents, said single general concept cannot be considered as novel, and the problem to be solved by the present application may be regarded as the provision of alternative markers whose methylation status is useful for predicting the responsiveness of a subject with a cell proliferative disorder of the breast tissues to a therapy comprising one or more drugs that target the estrogen receptor pathway or are involved in estrogen metabolism, production or secretion.

1.4 The solutions provided by the present application consist in the genes and sequences listed in the claims of the present application. In view of the prior art and of the differences in primary structure of said genes and sequences, and in view of the fact that no essential technical features could be distinguished which, in light of the prior art, could be regarded as a special technical feature in the sense of Rule 13.2 PCT that would provide a link between the plurality of solutions provided, the IPEA is of the opinion that there is no single inventive concept unifying inventions 1-191 as defined in the ISR in the sense of Rule 13.1 PCT. Consequently there is a lack of unity.

1.5 In addition, the relationship between the genes cited for instance in claim 1 and the nucleic acid sequences cited for instance in claim 25 is so unclear from the present

application and the subgroups of genes selected for instance in claims 2-14 or of nucleic acid molecules selected for instance in claims 26-29 are so intertwined that the ISA considered it an undue burden to establish the exact scheme of the claims corresponding to every single invention. Accordingly, the inventions 1-191 were divided as follows:

1.5.1 Invention 1: claims 1-80 (all partially); the subject-matter of claims 1-80 as far as it involves STMN1, and SEQ ID NO: 2003-2010.

1.5.1.1 Sub-invention 1.1: claims 1-80 (all partially); the subject-matter of claims 1-80 as far as it involves the sequence first mentioned in the claims, namely: SEQ ID NO: 27.

1.5.2 Inventions 2-27: claims 1-80 (all partially); the subject-matter of claims 1-80 as far as it involves:
- SFN, and SEQ ID NO: 2053-2060, for invention 2;
- S100A2, and SEQ ID NO: 1967-1968, 2045-2052, for invention 3;
- TGFBR2, and SEQ ID NO: 2095-2104, for invention 4;
- TP53, and SEQ ID NO: 1987-1986, 2041-2042, for invention 5;
- PTGS2, and SEQ ID NO: 2035-2038, for invention 6;
- FGFR1, and SEQ ID NO: 2031-2034, for invention 7;
- SYK, and SEQ ID NO: 2069-2078, for invention 8;
- PITX2, and SEQ ID NO: 1691-1692, 2025-2030, for invention 9;
- GRIN2D, and SEQ ID NO: 2087-2094, for invention 10;
- PSA, and SEQ ID NO: 1975-1976, 2011-2020, for invention 11;
- CGA, and SEQ ID NO: 1733-1736, 1977-1980, 2021-2024, for invention 12;
- CYP2D6, and SEQ ID NO: 2043-2044, 2127-2134, for invention 13;
- MSMB, and SEQ ID NO: 2039-2040, for invention 14;
- COX7A2L, and SEQ ID NO: 2105-2112, for invention 15;
- VTN, and SEQ ID NO: 2079-2086, for invention 16;
- PRKCD, and SEQ ID NO: 2061-2068, for invention 17;
- ONECUT2, and SEQ ID NO: 2119-2126, for invention 18;
- WBP11, and SEQ ID NO: 2135-2142, for invention 19;
- DAG1, and SEQ ID NO: 2113-2118, for invention 20;
- ERBB2, and SEQ ID NO: 1995-2002, for invention 21;
- TFF1, and SEQ ID NO: 1969-1974, for invention 22;
- TMEFF2, and SEQ ID NO: 1941-1946, for invention 23;
- ESR1, and SEQ ID NO: 1947-1954, for invention 24;
- RASSF1, and SEQ ID NO: 1981-1986, for invention 25;
- PSAT1, for invention 26;

- PCAF, and SEQ ID NO: 1925-1932, 1965-1966, for invention 27.

1.5.3 Inventions 28-159: claims 1-80 (all partially); the subject-matter of claims 1-80 as far as it involves:
- SEQ ID NO: 299-300, for inventions 28-29, respectivement;
- SEQ ID NO: 325-328, for inventions 30-33, resp.;
- SEQ ID NO: 331-332, for inventions 34-35, resp.;
- SEQ ID NO: 345-346, for inventions 36-37, resp.;
- SEQ ID NO: 381-382, for inventions 38-39, resp.;
- SEQ ID NO: 393-394, for inventions 40-41, resp.;
- SEQ ID NO: 401-402, for inventions 42-43, resp.;
- SEQ ID NO: 411-412, for inventions 44-45, resp.;
- SEQ ID NO: 417-418, for inventions 46-47, resp.;
- SEQ ID NO: 425-430, for inventions 48-53, resp.;
- SEQ ID NO: 443-444, for inventions 54-55, resp.;
- SEQ ID NO: 455-456, for inventions 56-57, resp.;
- SEQ ID NO: 475-476, for inventions 58-59, resp.;
- SEQ ID NO: 487-520, for inventions 60-93, resp.;
- SEQ ID NO: 573-574, for inventions 94-95, resp.;
- SEQ ID NO: 599-602, for inventions 96-99, resp.;
- SEQ ID NO: 605-606, for inventions 100-101, resp.;
- SEQ ID NO: 619-620, for inventions 102-103, resp.;
- SEQ ID NO: 655-656, for inventions 104-105, resp.;
- SEQ ID NO: 667-668, for inventions 106-107, resp.;
- SEQ ID NO: 675-676, for inventions 108-109, resp.;
- SEQ ID NO: 685-686, for inventions 110-111, resp.;
- SEQ ID NO: 691-692, for inventions 112-113, resp.;
- SEQ ID NO: 699-704, for inventions 114-119, resp.;
- SEQ ID NO: 717-718, for inventions 120-121, resp.;
- SEQ ID NO: 729-730, for inventions 122-123, resp.;
- SEQ ID NO: 749-750, for inventions 124-125, resp.;
- SEQ ID NO: 761-794, for inventions 126-159, resp.

1.5.4 Inventions 160-191: claims 1-80 (all partially); the subject-matter of claims 1-80 as far as it involves:
- SEQ ID NO: 40, for invention 160;
- SEQ ID NO: 122, for invention 161;
- SEQ ID NO: 43, for invention 162;

- SEQ ID NO: 74, for invention 163;
- SEQ ID NO: 127, for invention 164;
- SEQ ID NO: 86, for invention 165;
- SEQ ID NO: 90, for invention 166;
- SEQ ID NO: 128, for invention 167;
- SEQ ID NO: 105, for invention 168;
- SEQ ID NO: 115, for invention 169;
- SEQ ID NO: 121, for invention 170;
- SEQ ID NO: 126, for invention 171;
- SEQ ID NO: 129, for invention 172;
- SEQ ID NO: 125, for invention 173;
- SEQ ID NO: 132, for invention 174;
- SEQ ID NO: 123, for invention 175;
- SEQ ID NO: 131, for invention 176;
- SEQ ID NO: 130, for invention 177;
- SEQ ID NO: 124, for invention 178;
- SEQ ID NO: 68, for invention 179;
- SEQ ID NO: 50, for invention 180;
- SEQ ID NO: 91, for invention 181;
- SEQ ID NO: 92, for invention 182;
- SEQ ID NO: 99, for invention 183;
- SEQ ID NO: 83, for invention 184;
- SEQ ID NO: 41, for invention 185;
- SEQ ID NO: 78, for invention 186;
- SEQ ID NO: 137, for invention 187;
- SEQ ID NO: 133, for invention 188;
- SEQ ID NO: 134, for invention 189;
- SEQ ID NO: 135, for invention 190;
- SEQ ID NO: 136, for invention 191.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Subject of the present examination

1.1 In view of the non-unity objection raised by the ISA and of the fact that the applicant had an international search report (ISR) drawn for the first invention only, the subject of the present examination is the subject-matter of invention 1. Invention 1 has been defined in the ISR as claims 1-80 (all partially) as far as their subject-matter involves STMN1, SEQ ID NO:2003-2010 or SEQ ID NO:27. In view of the claims, it is clear that invention 1 includes subject-matter from the following independent claims: 1, 39, 40, 41, 44 and 80, and also directly or by way of dependency in the following dependent claims: 3, 4, 10, 12, 13, 15, 17, 18, 20-24, 42, 43, 45-62, 64, 65 and 67-77.

1.2 Further, document D3 has been cited against the novelty of claims 25-44 and 78-80, although claims 29-38 and 78-79 do not mention any of STMN1, SEQ ID NO:2003-2010 or SEQ ID NO:27. This is due to the fact that SEQ ID NO:299 was found to correspond to SEQ ID NO:27 where cytosines have been replaced by thymines (see also Re Item V, 3 below). Accordingly, the part of the subject-matter of those of claims 1-80 that involve SEQ ID NO:299 directly or by way of dependency, namely claims 25, 27, 28, 30, 32, 33, 35-39, 45, 47, 48, 50-61, 68-79 and 80 should be included in invention 1.

1.3 In view of the above, the subject-matter of claims 1, 3, 4, 10, 12, 13, 15, 17, 18, 20-25, 27, 28, 30, 32, 33, 35-62, 64, 65 and 67-80 involving STMN1, SEQ ID NO:2003-2010, SEQ ID NO:27 and/or SEQ ID NO:299 will be the subject of the present examination. No opinion is provided as to claims that do not involve said gene or sequences and thus have not been actually searched, namely 2, 5-9, 11, 14, 16, 19, 26, 29, 31, 34, 63 and 66.

2 Amendments (Art. 19 PCT)

2.1 The amendments filed with the International Bureau under Article 19(1) PCT do not introduce subject-matter which extends beyond the content of the application as filed, according to Article 19(2) PCT. In particular, the amendments carried out in claim 1 find a basis in the application as filed, for instance p. 17, l. 17-20 in combination with p. 18, l. 1-9.

3 Novelty (Art. 33(2) PCT)

3.1 Document D3 provides oligonucleotides and/or PNA-oligomers for detecting cytosine methylations as well as methods for the diagnosis and/or therapy of genetic or epigenetic parameters, in particular cytosine methylation, associated with tumour suppressor genes and oncogenes (p. 6, last paragraph).

3.2 D3 discloses a nucleic acid of SEQ ID NO:131 (6692 nt) that is 79% identical in a 6678 nt overlap with SEQ ID NO:27 (6680 nt), 100% identical to SEQ ID NO:299 (6680 nt) in a 6680 nt overlap, and comprises 12 additional nucleotides at the 5' end of the sequence. In fact, cytosines of SEQ ID NO:27 of the present application are replaced by thymines in SEQ ID NO:299, as in SEQ ID NO:131 of D3. D3 discloses also nucleic acids comprising a sequence of at least 18 nt in length of SEQ ID NO:131 (claim 1), oligomers (claim 3) comprising at least one CpG dinucleotide (claim 4), sets of oligomers (claim 6), sets of oligonucleotides where at least one is bound to a solid support (claim 9), and sets of oligonucleotides as primers for the amplification (claim 8).

3.3 Further, since SEQ ID NO:131 of D3 represents a chemically pretreated DNA corresponding to SEQ ID NO:27 of the application, using the oligomers or oligonucleotides of D3 for detecting the cytosine methylation state or single-nucleotide polymorphisms in the chemically pretreated DNA (including SEQ ID NO:131; p. 8-9. bridging paragraph) amounts to detecting cytosine methylation state or single-nucleotide polymorphisms in SEQ ID NO:27 after chemical pretreatment.

3.3.1 In addition, D3 discloses an arrangement of oligonucleotides or PNA-oligomers (array) arranged on the solid phase in the form of a rectangular or hexagonal lattice, wherein the solid phase is composed of any of the components indicated in claim 43 of the application (D3, p. 9, l. 6-13), and method for manufacturing said array (p. 9, l. 15-20). A kit comprising a bisulphite reagent and oligonucleotides as described in D3 is also disclosed (p. 9, last paragraph; claim 29).

3.3.2 Thus D3 takes away the novelty of claims 25, 27, 28, 30, 32, 33, 35-44 and 78. Accordingly, the present application does not meet the requirements of Art. 33(2) PCT.

4 Inventive step (Art. 33(3) PCT)

4.1 Since the additional reagents of kit claim 79 are standard in the art of performing

methylation assays (application p. 20, l. 1-8; p. 21, l. 20-22; p. 23, l. 12-13; claim 79), including such reagents in a known kit according to D3 which is also concerned with detecting methylation patterns is an obvious alternative. Therefore, the subject-matter of claim 79 does not involve an inventive step.

4.2 D3 discloses the use of products according to claims 25, 27, 28, 30, 32, 33, 35-44 and 78 for the diagnosis (i.e. characterisation, classification, differentiation) of diseases which have a connection with the genetic/epigenetic parameters of genes associated with tumour suppressor genes and oncogenes (p. 1, 2nd. paragraph), i.e. cancers. Claim 80, when related to the use of the products of claims 25, 27, 28, 30, 32, 33, 35-44 and 78 for the characterisation, classification or differentiation of breast cancer, differs from D3 in that the cancer considered is breast cancer. SEQ ID NO:27 of the application, of which SEQ ID NO:131 of D3 is the chemically-treated counterpart, corresponds to STMN1, which is a known marker of breast cancer (D5, D6, see Re Item V, 4.5.4 below). In view of this prior art, it is obvious to the skilled person that the primers and arrays disclosed in D3 may be used to characterise or classify breast cancer proliferative disorders. Accordingly, claim 80 does not involve an inventive step, contrary to the requirements of Art. 33(3) PCT.

4.3 In view of the above, the present application does not meet the requirements of Art. 33(3) PCT because the subject-matter of claims 25, 27, 28, 30, 32, 33, 35-44, 78, 79 and 80 does not involve an inventive step.

4.4 D4 is considered to represent the closest state of the art as to claim 1. D4 discloses methods for predicting the responsiveness of (breast) tumour cells to therapy, in particular to endocrine therapy, by assessing the status of the marker gene CGA, in particular the expression level (paragraphs [0008], [0013]).

4.5 The subject-matter of claim 1 differs from D4 in that the marker gene is STMN1 and the parameter assessed is the methylation pattern of said gene.

4.5.1 The problem to be solved by the subject-matter of claim 1 may be seen as providing an alternative method for predicting the responsiveness of a subject with a cell proliferative disorder of the breast tissues to endocrine therapy.

4.5.2 The proposed solution is the provision of a method comprising assessing the methylation pattern of STMN1.

4.5.3 D5 discloses that overexpression of stathmin (STMN1) in breast carcinomas is an

indicator of highly proliferative tumours. D6 discloses a correlation between stathmin (STMN1) expression in breast cancer with prognostic factors. None of said documents discloses a relationship between STMN1 expression and the methylation status of the gene.

4.5.4 Although it is known from document D7 that the analysis of CpG islands "has diagnostic potential and provides patient-specific methylation profiles that may predict those responsive to demethylation treatment" (p. 8380, col. 1), the skilled person could not have modified the method of D4 in order to arrive at the method of claim 1 without exercising inventive skills, since the prior art indicates that expression of STMN1 is related to the outcome of breast cancer but remains silent as to the possibility to use the methylation status of STMN1 as an indicator of responsiveness to endocrine treatment.

4.5.5 Accordingly, the subject-matter of the method claims 1, 3, 4, 10, 12, 13, 15, 17, 18, 20-24, 45-62, 64, 65 and 67-77 involves an inventive step in the sense of Art. 33(3) PCT. A claim according to claim 80 but limited to the use of said inventive method claims (see also Re Item III above) would also involve an inventive step.

5 Industrial applicability (Art. 33(4) PCT)

5.1 The subject-matter of claims 1-79 is considered to be industrially applicable. The subject-matter of claim 80, as far as it does not relate to methods for treatment of the human body by therapy (cf. Re item III above), is considered to be industrially applicable.